REMARKS

In view of the above amendments and the following remarks, reconsideration and further examination are respectfully requested.

Status of All of the Claims

Below is the status of the claims in this application.

1. Claim(s) pending: 46-51 and 55-60.

2. Claim(s) canceled: 1-45 and 52-54.

3. Claim(s) added: 59-60.

4. Claims withdrawn from consideration but not canceled: None.

The new and amended claims do not add any new matter, and are properly supported by the original disclosure in the application. Claims 46 and 55 were revised to be in independent form. Claim 50 has been amended to incorporate what were previously dependent limitations. Claims 56-58 were amended to be consistent with claim 55 from which they depend. New claim 59 depends from claim 50 and provides limitations found in other pending claims. New claim 60 is supported in the specification, including at page 18, the last line, to page 19, line 1.

Rejections Generally

Each of the claims pending in this application is related to freeze-dried formulations which "consist of" certain components, including FSH, LH and identified excipients. It has been found that such formulations provide surprising stability to the FSH/LH preparations, without the need for yet additional components. In the Office Action claims 24-41 and 55 were rejected under §102 as being anticipated by De Meere. Claims 42-49 and 56-58 were rejected under §103 as unpatentable over De Meere in view of Skrabanja and/or Franks. The rejected claims

24-45 have been canceled to simplify the issues under consideration, and the rejection of those claims is therefore obviated.

Request for Withdrawal of Finality of the Office Action

Rejections Under §102

Applicant requests the withdrawal of the indication of "finality" for the recent office action on the basis that the rejections under §102 are improper. Claims 24-41 and 55 were rejected as being anticipated by De Meere. However, De Meere can not anticipate these claims because De Meere does not disclose all of the elements set forth in these claims. All of these rejected claims call for the presence of an antioxidant, with certain claims further specifying that the antioxidant is methionine. Applicant is unable to find anything in De Meere, or in the statement of the rejections under §102, that addresses the presence of an antioxidant. The office action itself indicates that De Meere does not disclose antioxidants, stating at page 7, lines 4-5: "As presented supra, De Meere et al. teach all the elements of the formulations less the methionine." (Emphasis added) Applicant therefore submits that the stated rejections under §102 are improper and that these rejections, as well as the "finality" of the office action, should be withdrawn for this reason. (While only claim 55 of the claims rejected under §102 remains pending, this does not in any way change the conclusion regarding the impropriety of the rejections as to all of the identified claims.)

Rejections Under §103

Applicant requests the withdrawal of the indication of "finality" for the recent office action on the basis that the rejections under §103 are improper. Claims 42-49 and 56-58 were rejected as being unpatentable over De Meere in view of Skrabanja. However, the office action does not address the fact that claims 46-49 were directed to formulations which "consist of" the

indicated components. The office action noted in the §102 rejection that "If Applicant wants to specifically exclude the citric acid containing formulation [sic] should do so explicitly by choosing the limiting term consisting of." Applicant did use the term "consisting of" for claims 46-49, but the office action fails to address this fact in the §103 rejections. Instead, the office action acknowledges that both De Meere and Skrabanja disclose the use of citric acid salts as stabilizers, but does not indicate how a combination of these two references would result in a formulation that "consists of" components that do not include citric acid salts. Applicant therefore submits that the stated rejections of claims 46-49 under §103 are improper and that these rejections, as well as the "finality" of the office action, should be withdrawn for this reason.

Discussion of the Prior Art

The office action cites De Meere, Skrabanja and Franks in rejecting the claims. As background to Applicant's responses to the rejections, Applicant notes the following concerning these references.

DeMeere

The De Meere patent '132 has been cited as showing lyophilized gonadotropin-containing preparations containing a dicarboxylic acid salt stabilizer, as well as other constituents. De Meere emphasizes the need for the dicarboxylic acid salt stabilizer in order to achieve a suitably stable formulation. DeMeere indicates that:

> "A need exists for a gonadotropin containing pharmaceutical preparation which is stable over a sufficiently long period of time for the product to be manufactured, shipped, and stored prior to use. The need is especially great for a stable preparation containing more than one gonadotropin." Col. 1, lines 38-43.

DeMeere further indicates that stability is a particular problem for formulations including highly pure gonadotropins:

"Recently however, with the advent of more effective production and purification techniques, preparations of certain very pure gonadotropins are insufficiently stable. They degrade in a relatively short time, losing activity. In order to prevent or slow down this degradation, attempts were made to freeze-dry (lyophilize) the preparations. Lyophilization has only been partially successful however." Col. 1, lines 30-37.

"FSH purified from natural sources is generally only partially purified. The impurities seem to act to stabilize it somewhat. With rFSH, however the impurities are not present, and thus the FSH is more susceptible to rapid degradation and freeze-drying losses." Col. 2, lines 53-58.

The solution provided by DeMeere is the use of the salts of dicarboxylic acids to stabilize the formulations:

"Disclosed are lyophilized gonadotropin containing preparations containing a dicarboxylic acid salt stabilizer." Abstract, lines 1-3.

"Generally, the invention includes a gonadotropin containing lyophilized protein preparation which contains a dicarboxylic acid salt stabilizer. . . . The preparation will contain a sufficient amount of dicarboxylic acid salt to stabilize the gonadotropin in its freeze-dried form for a desired time at a desired temperature." Summary of the Invention, col. 1, lines 46-56.

DeMeere also teaches that formulations without the dicarboxylic acid salts are not stable. In Example I, DeMeere describes the preparation of two FSH samples with the difference (other than the concentration of the Tween 20) being that the first sample included sodium citrate and the second did not. The results indicate the instability of FSH in the absence of sodium citrate, stating:

"The first sample is stored for 3 months at 50°C., reconstituted with purified water, and analyzed by HPSEC. The resulting profile showed little oligomer formation. The second sample, not containing sodium citrate, was stored for 6 months at 50°C., reconstituted with purified water, and analyzed by HPSEC. The resulting profile showed much more oligomer formation.

The profile of the first sample showed no degradation products while the profile of the second sample showed almost exclusively oligomeric products." Col. 6, lines 45-56.

Similarly, FIG. 2 shows only a 40% recovery of activity of HCG after freeze-drying, and only a 5% recovery of activity after storage at 50°C, in the absence of a citrate salt.

DeMeere thus specifically teaches the need for the dicarboxylic acid salts, e.g., sodium citrate, in order to stabilize the FSH/LH formulations. The formulations may also include other excipients, including non-reducing salts (e.g., sucrose) to increase the "collapse temperature", and anti-adsorption agents (e.g., Polysorbates) to prevent adsorbance of the protein to the container walls. The use of sodium biphosphate is also mentioned. But in each instance, sodium citrate or the like is included.

Skrabanja

Similarly, Skrabanja '945, primarily focused on liquid preparations, describes formulations including FSH, LH and/or other gonadotropins which are stabilized with dicarboxylic acids/salts:

> "The invention relates to a liquid gonadotropin-containing formulation which comprises a gonadotropin and stabilizing amounts of a polycarboxylic acid or a salt thereof and of a thioether compound." Page 3, lines 15-16.

Skrabanja also indicates that stability is a particular problem for formulations including highly pure gonadotropins:

> "With recFSH, however the impurities are not present and thus the FSH, being present in comparatively low concentration on the basis of protein is more susceptible to rapid degradation." Page 3, lines 53-54.

While Skrabanja mentions the use of disaccharides, such as sucrose, it does so in the context of formulations which first include the polycarboxylic acid or salt and the thioether:

> "It has been found that the incorporation of a nonreducing disaccharide, such as sucrose or trehalose, into a formulation, which already comprises a polycarboxylic acid, or a salt thereof, and a thioether compound as stabilizers, further increases the stability of the gonadotropin in the liquid formulation." Page 4, lines 16-18 (emphasis added).

Franks

Franks is primarily cited for the proposition that formulations of gonadotropins are known to be provided in unit-dose or multi-dose containers, for example sealed ampoules and vials, and that they may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Applicant submits that Franks does not otherwise provide a teaching that would render the present claims obvious.

Responses to the Claim Rejections

General Discussion

The claimed invention is directed generally to freeze-dried formulations which include several identified components, namely FSH, LH, a surfactant, a stabilizer and tonicity agent, an antioxidant, and a phosphate buffer. More specifically, by the present amendments all of the claims are limited to formulations which "consist of" these components. By contrast, the cited art specifies the presence of a polycarboxylic acid or salt thereof.

A critical issue addressed by this invention is the provision of freeze-dried formulations of FSH and LH which are stable. The present application, and the cited art, notes the problem in the art of providing FSH/LH formulations which are sufficiently stable over time. One approach in the prior art has been to freeze dry the formulations for reconstitution at a time closer to the time of administration. However, it has remained a problem in the art to provide a freeze-dried formulation which itself is sufficiently stable.

DeMeere and Skrabanja both provide the same answer to the problem. Both call for the presence of a polycarboxylic acid, or salt thereof, to stabilize the freeze dried preparations.

Without it, DeMeere obtained "almost exclusively oligomeric products," which of course are not suitable for treatment purposes.

Rejections Under §102

Claims 24-41 and 55 were rejected as being anticipated by De Meere. Claims 24-41 have been canceled to reduce the issues in this case. Claim 50 has been amended to change the transitional phrase from "consisting essentially of" to "consisting of". New claims 59-60 have been added. Applicant submits that all of the pending claims are novel over the De Meere reference.

As previously noted, these claims are not anticipated by De Meere because that reference does not disclose all of the elements set forth in these claims. All of these claims call for the presence of an antioxidant, with certain claims further specifying that the antioxidant is methionine. De Meere does not disclose the use of antioxidants, and this fact is acknowledged in the office action. See page 7, lines 4-5, quoted above. Applicant therefore submits that claim 55 and all of the other pending claims are novel over De Meere.

These claims are further distinguished over the cited art in that they relate to formulations "consisting of" the identified components. The office action notes that the term "consisting of" would "specifically exclude the citric acid containing formulation" of De Meere (and therefore of Skrabanja). Office Action, page 5, lines 17-19. This distinction from De Meere comes from the fact that there is no teaching in De Meere as to any formulations not including a dicarboxylic acid salt. The reference is in fact focused on the use of dicarboxylic acid salts to provide stability. Without such salts, DeMeere obtained "almost exclusively oligomeric products," a sign of an unstable product. Since all pending claims use the "consisting of" term, it is submitted that

said claims are novel over De Meere. They are similarly novel over Skrabanja for the same reason.

Claims 47-51 and 56-59 are directed to formulations which include recombinant, human FSH and LH. The cited art indicates that stability of highly pure, recombinant FSH and LH is even more difficult to accomplish. The significance and novelty of the present invention is therefore even greater with respect to the formulations covered by those claims.

The office action referred to the fact that De Meere emphasizes the use of citric acid providing for stable formulations that are kept in storage for months, and noted that the instant claims do not include such a limitation. In response, applicant has added claim 60 which specifically claims formulations having heightened stability for nine months, without including the dicarboxylic acids/salts relied upon in De Meere and Skrabanja to achieve stability. This claim is further distinguished on that basis.

Rejections Under §103

Claims 42-54 and 56-58 were rejected as being unpatentable over De Meere in view of Skrabanja and/or Franks. Claims 42-45 and 52-54 have been canceled, and the rejections of those claims are therefore obviated. Claim 50 has been amended to change the transitional phrase from "consisting essentially of" to "consisting of". New claims 59-60 have been added. Applicant submits that all of the pending claims are unobvious over De Meere and Skrabanja/Franks.

As previously noted, claims 46-49 are directed to formulations which "consist of" the indicated components. The office action fails to present a prima facie case of obviousness as to these claims because it does not address the "consisting of" language in the §103 rejections. There is no teaching in De Meere or Skrabanja as to how these references could be combined

without the resulting formulations including dicarboxylic acids, and/or salts thereof. Both references in fact are focused on the use of dicarboxylic acids and/or salts to provide stability, and therefore any combination expected to provide stabile formulations would certainly include dicarboxylic acids and/or salts. Applicant therefore submits that claims 46-49 are unobvious over De Meere in view of Skrabanja. Further, the other remaining claims 50-51 and 55-60 also use the "consisting of" language, and it is submitted that they are unobvious over the cited art for the same reason.

It should be understood that the above remarks are not intended to provide an exhaustive basis for patentability, but are simply provided to overcome the rejections made in the Office Action in the most expedient fashion. In view of the above amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and an early notice of allowance is earnestly solicited.

If after reviewing this amendment the Examiner feels that any issues remain which must be resolved before the application can be passed to issue, the Examiner is invited to contact the undersigned representative by telephone to resolve such issues.

Respectfully submitted,

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